

I. INTRODUCTION

This Regulatory Impact Analysis (RIA) examines the incremental costs, benefits, and other impacts of regulation under Section 5 of the Toxic Substances Control Act (TSCA) as set forth in the rule on Microbial Products of Biotechnology. As an introduction to the analysis, this chapter briefly discusses events leading up to the rule, contrasts key elements of current oversight policy with the rule, and provides a summary of regulatory requirements. An overview of the remaining chapters of the RIA is also presented.

A. Background

For many years, microorganisms have been employed by numerous businesses, universities, and governmental bodies to meet certain research and commercial needs. The majority of these microorganisms and microorganism products have been developed for use in application areas that fall outside the jurisdiction of TSCA and are specifically excluded in the Act (medical, food and beverage, and pesticide applications). However, there are a number of application areas that are not excluded and, although EPA is unable to estimate precisely the magnitude of these activities, it is believed that they may constitute about 10 percent of the overall market for biotechnology products.

This figure reflects the share of overall R&D spending in biotechnology dedicated to TSCA-related markets (see Chapter II), including treatment of biological waste, production of enzymes and other chemicals in contained

fermentation systems, and field applications of microorganisms to enhance nitrogen fixation on crops such as soybeans and alfalfa.*

During the past two decades, a number of organizations have used genetically modified microorganisms in commercial enzyme production, or other TSCA applications. Although most of these modified microorganisms are similar in their traits to naturally occurring microorganisms, uncertainty about novel behaviors that could be exhibited by some microorganisms in the environment has led to the concern that, in some instances, they may present a risk to human health or the environment.

As a result of these risk concerns, EPA announced a policy regarding Premanufacture Notice (PMN) reporting for general commercial use that is, use for commercial purposes other than research and development (R&D) of certain genetically modified microorganisms in 1986 (EPA 1986b).** EPA also requested voluntary reporting for R&D uses of microorganisms involving introductions into the environment.

Certain differences exist, however, between the current regulatory environment, as defined by the Agency's 1986 Policy Statement, and the regulatory environment associated with the rule. These differences are highlighted below.

It should be noted that other Agencies, such as the Food and Drug Administration, have had statutory authority to oversee certain sectors of the biotechnology industry (e.g., pharmaceuticals) for a somewhat longer period of time than EPA has had under TSCA. Although microorganisms were reported to the initial TSCA Inventory in 1978, EPA's first policy initiative specific to biotechnology products subject to TSCA was issued in 1984, at which time the Agency proposed a new mechanism for review of genetically engineered and nonindigenous microbial pesticides (regulated under FIFRA) as well as its plan for addressing certain genetically engineered microorganisms under its chemical premanufacture notification program (regulated under TSCA).

This policy is summarized in the following section.

B. Current Policy and the Final Rule

EPA believes the rule to be preferable to continued oversight of microorganisms under the Agency's 1986 Policy Statement, as the rule introduces mechanisms into the Agency's regulatory program to specifically tailor approaches/procedures appropriate to microorganisms and allow partial exemption from premanufacture reporting in cases where there is less uncertainty regarding the behavior of certain microorganisms possessing such traits.

It is important that the differences between the 1986 Policy Statement and this rule be clear if an appreciation for the impact of the rule on EPA's regulatory program under TSCA is to be gained. Therefore, to facilitate an understanding of the relationship between the current policy and the rule, the two oversight schemes are compared below.

Under current policy, industry is required to file with EPA a premanufacture notice (PMN) in connection with any new microorganism before it is manufactured, imported, or processed and intended for general commercial use, where a "new" microorganism is defined as any intergeneric microorganism not found on the TSCA Chemical Substance Inventory. More specifically, under this policy, new microorganisms are defined as "intergeneric" microorganisms, which are microorganisms created through the deliberate combination of genetic material originating from organisms in different genera. Exclusions are made only for those intergeneric combinations in which the genetic material added to the recipient microorganism consists solely of well-characterized, non-coding regulatory regions. The intergeneric definition implicitly excludes naturally occurring microorganisms and genetically modified microorganisms other than intergenerics. Current policy does not distinguish between closed-system, or fermentation applications, and field, or environmental

applications, with respect to PMN reporting requirements at the general commercial use level.

In contrast to the uniform reporting requirements applicable to products intended for distribution in commerce, intergeneric microorganisms intended for use in commercial R&D are treated somewhat differently, under current policy. In general, under section 5(h)(3) of TSCA, new chemical substances produced in small quantities and solely for purposes of research and development are exempt from PMN reporting requirements, with EPA interpreting what constitutes a "small quantity." For traditional chemicals, this interpretation refers to those chemical substances in quantities of 10,000 kilograms or less per year (40 CFR Part 723). This interpretation effectively exempts all R&D from section 5 reporting requirements. Microorganisms can reproduce, however, and EPA finds it appropriate to define what constitutes a small quantity for living organisms differently than for traditional chemicals. In the case of an experiment involving environmental release of new microorganisms, under current policy, EPA has requested voluntary PMN reporting by researchers for all tests. Alternatively, EPA has not requested voluntary reporting for microorganisms intended for use in R&D conducted in contained structures.

The rule introduces some important modifications to this oversight strategy. These changes will be highlighted briefly here, and described in greater depth in the following section.

First, with regard to reporting requirements at the general commercial use level, the rule incorporates exemption provisions to allow for reduced burden in cases where there is less uncertainty about a new microorganism's phenotypic traits. More specifically, eligibility for such exemptions is linked to requirements regarding use of well-defined genetic material; a

parental microorganism with a history of safe use; and appropriate containment. (These exemptions have been designated Tier I and Tier II exemptions, and are described in section C below.) These exemption provisions are expected to have a major impact on the burden required in both preparing and reviewing a significant number of notification submittals, resulting in a significant cost savings to both industry and government.

The rule also alters EPA policy with regard to research and development (R&D) uses involving testing of microorganisms in the environment. Under the rule, reporting would no longer be voluntary for new microorganisms subject to oversight. However, researchers are allowed to satisfy notification requirements by utilizing a more flexible reporting format, (identified as TSCA Experimental Release Application, or TERA) rather than the PMN. Also, provisions exist in the rule to permit certain research activities with specific microorganisms to qualify for exemption even from TERA reporting requirements. The impact of these changes will be to ensure that more frequent notification will be made in cases where novel microorganisms will be involved in field research for commercial purposes.* To the extent that voluntary filing has not occurred, overall burden would be expected to increase. (Though this increase may be limited due to future exemptions).

Additionally, requirements in connection with "contained structure" exemptions involve limited additional recordkeeping relative to requirements under current policy in connection with "small quantities" exemptions. Only researchers performing contained R&D are eligible for the "contained

EPA considered alternative definitions of "commercial purposes," with implications ranging from capturing only those cases where, as determined by the researcher, one or more indicia of commercial intent are present to capturing all environmental research. The former, determined least burdensome by the Agency, was selected.

structure" exemption. (See Section 2 below for details regarding eligibility requirements).

Finally, the rule also contains provisions allowing for interagency deferral, to avoid duplicative oversight of research and development activities.

C. Overview of Regulatory Requirements

The requirements contained in the provisions of the rule vary depending on the type and stage of development of a commercial microorganism. Therefore, a summary of the regulatory requirements can be presented by first examining how the rule defines the regulated community and then describing the requirements in relation to the two major developmental stages of new microorganisms intended for commercial purposes: R&D and general commercial use. Thus, three subsections follow: regulatory oversight; microorganisms in commercial research and development; and microorganisms in general commercial use.

1. Regulatory Oversight

"New" microorganisms* intended for commercial purposes are subject to TSCA Section 5(a)(1) reporting requirements, and thus subject to this rule. PMN reporting under the current interpretation of new under TSCA would be required for commercial products, because "new" microorganisms are considered to be "new" chemical substances. Under the 1986 Policy Statement, "new" (not on the inventory) is defined to mean intergeneric microorganisms;

Under current policy, "new" is defined to mean intergeneric microorganisms that are not on the inventory of existing chemical substances (microorganisms currently are defined to be chemicals under TSCA). Some microorganisms are implicitly considered to be on the inventory, while others are explicitly listed. Those intergeneric microorganisms that are not implicitly or explicitly included are considered "new".

that is, microorganisms combining genetic material from organisms in different genera.

The definition will not change under the rule. Thus microorganisms subject to oversight under current policy will continue to be subject to oversight under the rule.*

Exemptions and exemption mechanisms, however, have been included in the rule. That is, not all new microorganisms subject to TSCA are subject to full reporting. These mechanisms allow for less burdensome or more flexible notification schemes. Each reporting exemption corresponds to a specific point in the product development process, and will be addressed below in that manner.

With regard to the Agency's definition of "commercial purposes," the proposed rule described three alternative approaches for oversight of biotechnology R&D under TSCA. One alternative defined commercial purposes based on a set of commercial indicia; thus, whether a project is intended for commercial purposes would be determined by the researcher. This alternative has been incorporated into the rule, and minimizes burden by limiting the rule's coverage to only those cases where commercial intent is pre-determined.

2. Microorganisms in Commercial Research and Development

Organizations manufacturing, importing, or processing "new" microorganisms intended for use in commercial research and development (R&D) in the environment will be subject to reporting under the rule. Full Microbial Commercial Activity Notice (MCAN) reporting will not be required for

It should be noted that once a microorganism has been placed on the TSCA Chemical Substance Inventory by EPA, it is no longer "new;" however, submitters desiring to use the microorganism in a manner which represents a significant new use are subject to notification when EPA issues a Significant New Use Rule (SNUR) for the particular substance.

such activities. In lieu of the MCAN, a TSCA Experimental Release Application (TERA) will be accepted. In addition, all submitters commencing work following EPA approval will be required to retain for three years following the commencement date the following records:

- all data submitted with TERA/MCAN;
- date of commencement of testing, manufacture, import, or processing; and
- volume of import, testing, or processing for the first three years.

A summary of R&D activity within one year of termination of such activity will also be required to be submitted in connection with TERA approvals. The rule also provides a mechanism for EPA to supplement documentation requirements with additional restrictions, such as monitoring, in connection with a TERA approval.

In addition to the TERA, three additional mechanisms have been incorporated into the rule to reduce reporting burdens in connection with microorganisms intended for use in commercial R&D. First, exemptions from R&D reporting may be developed in the future for intentional testing in the environment of specific strains in addition to Rhizobium meliloti and Bradyrhizobium japonicum (both of which have been the subject of voluntary PMNs). This reporting exemption, referred to as "TERA Exempt," is expected to be expanded in the future as EPA gains more knowledge about releases involving specific modified microorganisms.

Second, R&D experiments conducted within a contained structure (e.g., a laboratory or greenhouse) may be eligible for an exemption and would not be subject to mandatory reporting. Entities eligible for these "contained structure" exemptions will be required to maintain records supporting such eligibility. The records, in some cases, would include a description of

prudent laboratory practices used and records describing the selection and use of containment and/or inactivation controls. However, the majority of the time, it is expected that researchers will be abiding by, and following the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules ("NIH Guidelines"). In this case, the recordkeeping requirements of the exemption may be met by simply documenting that the TSCA work is to be conducted in accordance with the Guidelines, imposing little additional burden. At the Agency's request, entities would be required to provide records to EPA. If changes in control protocols were mandated by EPA upon review of these records, entities would be required to amend existing controls appropriately.

The third reporting exemption mechanism applies in cases where another federal agency has oversight responsibility for a particular R&D activity. Where appropriate, in cases involving R&D performed within a contained structure system and under federal sponsorship, EPA would defer oversight to the sponsoring agency, since the NIH Guidelines must be followed as a condition of continued financial support by any Federal agency. This provision eliminates duplicative oversight.

Initially EPA proposed requiring "upfront" substantiation of confidential business information (CBI) claims, (that is, a CBI claim would need to be accompanied by evidence substantiating the claim when a notice is submitted to EPA). An alternative stipulation requiring substantiation upon EPA request, for example, in the event that a Freedom of Information Act (FOIA) request is received, has been incorporated into the rule for CBI claims filed in association with a TERA.

3. Microorganisms in General Commercial Use

EPA requires a MCAN for all "new" microorganisms manufactured, imported, or processed for general commercial use (defined as use for commercial purposes beyond R&D). As required for microorganisms in commercial R&D, all submitters filing a MCAN and commencing work must retain documentation of all data contained in the MCAN submission, as well as the date of commencement and volume of manufacture or import, for three years following the commencement date. Submitters commencing work may also be bound by restrictions as set forth in a consent order, if such an order is deemed necessary by the Agency.

Three mechanisms, all in the form of reporting exemptions, have been incorporated into the rule to reduce regulatory burdens at this stage of product development. First, the Test Marketing Exemption (TME) may be appropriate for test market operations. (The TME provision of the rule is the same as for current requirements in the PMN program.) Information requirements are similar to the MCAN, but the TME process is completed in only 45 days, as opposed to 90 days for the MCAN. Submitters eligible for this exemption must retain documentation of compliance with any restrictions imposed by EPA in connection with TME approval. This documentation must be retained for three years from the final date of manufacture or import under the exemption.

The second and third mechanisms allow for reporting exemptions for certain "new" microorganisms in general commercial use. The exemptions would take the following forms:

- Tier I, involving one-time certification only; and
- Tier II, involving expedited review, with less information required than for a full notification.

Specific microorganisms are eligible for the Tier I or Tier II exemptions. These are microorganisms EPA has determined to be low risk with respect to the characteristics of the recipients, and users must comply with any prescribed measures for the introduced genetic material and for minimizing microorganism emissions from the contained facility in which they are used. The Tier I exemption would require the submitter to certify in writing in a one-time report that compliance with the requirements for the exemption have been satisfied, and recertification is not required for additional work involving the same recipient organism in the same facility. The Tier II exemption will involve limited reporting, focused on containment and inactivation procedures.

In addition to the general recordkeeping requirements outlined above, submitters eligible for these exemptions will also be required to maintain records supporting such eligibility.

CBI substantiation requirements for microorganisms in general commercial use have been incorporated into the rule. That is, "upfront" substantiation will be required for activities intended for general commercial use.

4. Significant New Uses of Inventoried Microorganisms

The rule also includes a procedure for identifying microorganisms for significant new use reporting in the future. However, no significant new use rules have been included at this time.

D. Structure of the RIA

This introductory chapter is followed by seven additional chapters. Each chapter is briefly discussed below, with methodological approaches and/or key data sources noted.

1. Chapter II

Chapter II describes the organizations and products that make up the regulated community. The chapter also includes a discussion of the biotechnology applications subject to regulation under TSCA. Key sources of data include the Agency's 1987 survey, historical profiles of actual submissions received over the course of EPA's biotechnology program, and recent studies assessing current market trends in microbial products.

2. Chapter III

Chapter III presents a discussion of the benefits of the rule. The effectiveness of the rule in reducing risk is demonstrated by its ability to allow regulators to access those informational elements necessary to evaluate potential hazards posed by novel behaviors of certain "new" microorganisms. Also, a qualitative analysis is provided which describes the sources of benefits expected to accrue under the rule. A concluding discussion characterizes the expected benefits, which result from the rule's ability to minimize social costs arising from potential harm to human health and environment and to improve regulatory efficiency.

3. Chapter IV

Chapter IV describes the methodology used for computing the incremental costs to industry of the rule. Estimates are presented for the first and fifth years following promulgation.

In developing its estimates, the Agency first estimated the particular mix of reporting vehicles and/or documentation/recordkeeping burdens associated with each regulatory alternative. Next, each reporting vehicle or documentation/recordkeeping requirement was evaluated separately with respect to potential cost impact. The total incremental costs associated with each

regulatory alternative were then calculated by grouping the appropriate mix of unit costs associated with each respective regulatory alternative.

Unit costs for reporting vehicles were estimated based largely on a cost analysis report prepared for EPA by SRI International. EPA incorporated information from submitters of voluntary microorganism notifications and the expert judgement of Agency scientists into these burden estimates to ensure that tasks for which costs were estimated reasonably coincided with requirements under the rule.

In addition to costs resulting from reporting or recordkeeping provisions, costs may also be incurred in response to restrictions placed on the submitter as a condition of Agency approval. One such restriction could be monitoring requirements. Other costs were not quantifiable, such as the costs associated with impacts on innovation or delays in product development due to the time required for adequate EPA review of the various reporting vehicles. Such impacts are addressed in later sections of the RIA (see Appendix F).

4. Chapter V

Chapter V examines the incremental cost impact to the government in connection with the rule. Agency costs included expenses incurred in association with meetings of an expert review panel and costs associated with the review of submissions by EPA personnel.

In estimating Agency costs, EPA relied on experience acquired during its reviews of submissions received under current regulatory authority. Also, EPA currently receives a fee from each submitter to cover costs of review. Since a fee schedule has been incorporated into the rule, Agency costs were reduced by the total estimated amount of collected fees.

5. Chapter VI

Chapter VI presents a qualitative examination of the effects of the rule on innovation activity based on information on costs provided by submitters of voluntary notifications. This chapter connects the rule to the ultimate effects imposed by the rule on the nation's welfare. The direct effects of the rule are to increase the cost and time to develop new products. These direct effects also create indirect effects on the numbers of new products developed and the nature of those products. These indirect effects, in turn, can affect the economy as whole and the welfare of society.

6. Chapter VII

Chapter VII considers the possible effects of the rule on international competitiveness, based on the examination of current biotechnology regulatory activity in the European Community, Japan, and Canada. However, due to the uncertainty associated with the outcomes of current regulatory initiatives being developed in foreign countries, reaching conclusions regarding the impact of the rule on the competitive position of U.S. companies in world markets is difficult.

7. Chapter VIII

Chapter VIII presents the Agency's Regulatory Flexibility Analysis. This analysis includes an estimate of the number of small businesses within the industry and the magnitude of regulatory impact on such businesses. This section also presents regulatory alternatives for small businesses including a reduction of upfront CBI substantiation requirements, elimination of filing fees, and other possible options, as well as the Agency's final assessment of small business impacts.

In addition, nine appendices have also been prepared, providing additional background information and computational details.